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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,651	07/07/2006	Philip C. Trackman	BU-112XX	5481

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,651	TRACKMAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *8-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/09/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

With supplemental amendment, filed 11/9/09, in response the office action, mailed on 7/8/2009, the applicants amended claims 1 and 4-6. Claims 1-15 are currently pending in the instant application. Claim 8-15 remain withdrawn.

Applicants' arguments filed on 11/9/09, in response to a previous office action mailed on 7/8/2009, have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejection 35 U.S.C 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2--7 (dependent on claim 1) remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the following reason: The term "polypeptide comprises a therapeutical active portion of a lysyl oxidase pro-peptide" in the claims indicates that the therapeutical active portion belongs to the pro-peptide. The term "wherein said polypeptide is active in inhibiting cell growth or proliferation..." is not providing the therapeutical activity of the pro-peptide but rather the activity of the polypeptide that COMPRISES the pro-peptide. Therefore, the claims remain indefinite with regard to the term "therapeutical active portion of a lysyl oxidase pro-peptide".

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for following reason: In part a) the claim now recites "polypeptide comprising a lysyl oxidase pro-peptide". Parts b), d) and f) recite "fragment of said lysyl oxidase pro-peptide polypeptide. Is the lysyl oxidase pro-peptide polypeptide of parts b), d) and f) the same as the "polypeptide comprising a lysyl oxidase pro-peptide" of part a)? Should the fragment of parts b), d) and f) be a fragment of the pro-peptide since the preamble of the claim refers to the identification of a therapeutically active portion of a lysyl oxidase PRO-PEPTIDE? There is a discrepancy in part f) also between the preamble and what is determined in part f) because the preamble refers to the identification of a therapeutically active portion of the pro-peptide whereas part f) is concerned with the determination of an active portion of a lysyl-oxidase pro-peptide polypeptide. A portion of a polypeptide comprising the pro-peptide is not the same as a portion of the pro-peptide.

Claim Rejection 35 U.S.C 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention as explained in prior office action and stated again below:

Claims 1-5 are directed to a therapeutic composition comprising the active portion of any lysyl oxidase pro-peptide lacking enzymatic activity from any source having any structure (claims 1-3) or any lysyl oxidase pro-peptide variant (claims 4-5) wherein said variant comprises an amino acid sequence which results from any number of conservative substitutions in any one of SEQ ID NO: 1-8. The specification teaches the structure of only a few representative species of such lysyl oxidase pro-peptides and fragments thereof lacking enzymatic activity, i.e., the human polypeptides of SEQ ID NOs: 1, 3 and 6; the mouse polypeptides of SEQ ID NOs: 2, 4 and 7, and the rat peptides of SEQ ID NOs: 5 and 8. SEQ ID NOs: 1 and 2 are full length lysyl oxidase pro-peptides and SEQ ID NO: 3-8 are fragments of human, rat and mouse lysyl oxidase pro-peptides comprising 35-38 amino acids. The specification fails to describe any other representative species by any identifying characteristics or properties other than the biological activity lacking enzymatic activity. Prior art teach a small number of species having lysyl oxidase activity (EC 1.4.3.13 in EXPASY search results attached). In view of the fact that a structural/functional correlation that would allow one of skill in the art to envision the structure of additional lysyl oxidases is unknown, and the number of known species is small, one cannot reasonably conclude that the structural features required in any protein having lysyl oxidase activity are adequately described by the specification and/or the art.

Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In the instant case the scope of the instant claims encompass a genus of polypeptides which are lysyl oxidase pro-peptides lacking enzymatic activity from any source or any variant comprising an amino acid sequence that results from making any number of conservative substitutions in SEQ ID NOs: 1-8, wherein said variants can have any activity. The claimed therapeutic composition comprises a polypeptide **having any structure**. The prior art, as evidenced by WO/0185157, teaches a few lysyl oxidases and the specification teaches (page 3) three lysyl oxidase pro-peptides and fragments thereof(SEQ ID NOs: 1-8). However, the specification fails to describe any other representative species by sufficient identifying characteristics or properties to show that applicant was in possession of the claimed genus.

Argument

Applicants arguments against rejection of claims 1-5 under 35 U.S.C. 112, first paragraph written description are acknowledged but are not found persuasive because as explained in the prior rejection and above, knowledge of the structure of the lysyl oxidase is essential to find out which portion of the pro-peptide is therapeutically active, without such knowledge it is not possible to find out the recited active portion. Furthermore, while the claims encompass structural variants of any lysyl oxidase pro-peptide, the specification and the art are completely silent with regard to the structural

features required in any of these variants such that they can have cell growth inhibiting activity. There is no structure/function correlation which would allow one of skill in the art to determine the structural variations that can be made to any lysyl oxidase pro-peptide and observe cell growth inhibition. Therefore the specification fails to sufficiently describe the claimed invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic composition comprising any of the peptides of SEQ ID NOs:1-8, and a method of identifying the minimum portion of the lysyl oxidase pro-peptides of SEQ ID NO: 1 or 2 which has cell growth inhibiting activity, , does not reasonably provide enablement for (A) any therapeutic composition comprising (1) any lysyl oxidase pro-peptide or fragments thereof, or (2) any structural variant of the polypeptides of SEQ ID NO: 1-8 having any activity, wherein said variant is the result of any number of conservative substitutions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the claims: Claim 1-5 are broadly directed to include (A) any therapeutic composition comprising (1) any lysyl oxidase pro-peptide or fragments thereof, or (2) any structural variant of the polypeptides of SEQ ID NO: 1-8 having any activity, wherein said variant is the result of any number of conservative substitutions.

The state of the prior art; the relative skill of those in the art; and the predictability or unpredictability of the art:

Neither the specification nor the state of the art at the time of the invention provided the necessary guidance for (1) correctly identifying based solely on structural features which proteins from any source have lysyl oxidase activity so that their pro-peptide can be identified, or (2) altering the amino acid sequence of any lysyl oxidase pro-peptide to obtain a peptide which would have cell growth inhibiting activity. There is no guidance as to which positions within SEQ ID NO: 1-8 can be tolerant of conservative substitutions and which amino acids can be used as substitutes so that the recited variants can also inhibit cell growth. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the same desired biological activity. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

The amount of direction provided by the inventor; and the existence of working examples: The specification fails to provide any specific guidance for obtaining any lysyl oxidase or its corresponding pro-peptide, nor does it provide any guidance as to which conservative modifications can be made to any of the peptides of SEQ ID NO: 1-8 such that they would display cell growth inhibiting activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention and the specification provides general teachings for searching and screening for the claimed invention, it was

not routine in the art to screen by a trial and error process for all polypeptides having lysyl oxidase activity and their corresponding pro-peptides, nor was it routine in the art to make an infinite number of structural variants and test them for a desired activity.

Argument

Applicants arguments against the rejection of claim 1 under 35 U.S.C. 112, first paragraph enablement requirement are not found persuasive Identification of any lysyl oxidase pro-polypeptide will require knowledge of the structure of such lysyl oxidase. The claim requires any lysyl oxidase pro-peptide from any source. However, neither the specification nor the art provide any guidance as to the structures of all the lysyl oxidase pro-peptides required nor do they provide any teaching or suggestion as to how the ones disclosed in the specification and/or the prior art correlate with any lysyl oxidase pro-peptide.. Applicants argue that one of skill in the art can use conservative substitutions to find out the active portion of a lysyl oxidase pro-peptide. This is not found to be persuasive. Examiner acknowledges the referred article of J. of Mol. Evolution, 1983, 19, pp 171-175. However, the argument found to be unpersuasive. The reference of Witkowski et al. (Biochemistry. 1999 Sep 7; 38(36): 11643-50; PTO 892) teaches that only a single amino acid substitution results in conversion of the activity of a polypeptide to a second, distinct activity (see e.g., Table 1, page 11647). Also, Examiner would like to refer to the EXPASY printout to show (attached herewith) that only 6 lysyl oxidases are known and that it would be undue experimentation to determine the structure of all lysyl oxidases when no structure/function correlation is

known and there is no indication as to which are the structural features required in any lysyl oxidase or the structural features required in the pro-peptide of any lysyl oxidase. Although the actual enzymatic activity was well known in the art, the issue is not whether one of skill in the art would not know what a lysyl oxidase does but how to obtain the pro-peptide of any lysyl oxidase or how to make the pro-peptide of any lysyl oxidase without undue experimentation when only 6 species are known and there is no teaching or suggestion as to which are the essential structural features required in a lysyl oxidase or its pro-peptide such that one could identify or make such protein without undue experimentation. Therefore without any knowledge of how the structure of any lysyl oxidase pro-peptide correlates with the ability to inhibit cell growth, the effect of making any number of conservative substitutions is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejection - 35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 remain rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (WO/0185157, November 15, 2001). Li et al teach a therapeutic composition comprising a lysyl oxidase polypeptide without catalytic activity for the treatment of cancer/tumors (page 10 lines 25-33, and page 13, lines 25-28).

Applicants' arguments presented at pages 13-17 of the response filed on 4/7/2009 traversing the instant 35 U.S.C. 102(b) rejection have been considered but not found to be persuasive because Li et al teach a lysyl oxidase which may **not have catalytic activity but is therapeutically active (**page 13, lines 25-28) . The lysyl oxidase of Li et al. having no catalytic activity would include the pro form of the enzyme (pro-peptide linked to the mature enzyme). Since claims 1-3 are directed to a composition that has a polypeptide that comprises the pro-peptide, the pro-form of the lysyl oxidase (LO) of Li et al. having no catalytic activity, is a species of the genus of polypeptides comprising the pro-peptide recited in claims 1-3. Applicants' argument about Li et al teach the therapeutic activity linked to catalytic activity is considered. However Li et al also teach that said therapeutic activity can be attributed to lysyl oxidase which may **not have catalytic activity.** Since Li et al teach **"fragments and/or derivatives pf LO and/or its homologs, with or with out catalytic activity",** Li et al teach a polypeptide that comprises the pro-peptide, the pro form of the lysyl oxidase of Li et al. having no catalytic activity. Limitations regarding inhibition of cell growth in agar or in inhibition of tumor formation are inherent to the pro form of the lysyl oxidase of Li et al as evidenced by the specification which teaches that the lysyl oxidase pro-peptide has those activities. As such, the teachings of Li et al. anticipate the instant claims as written.

Allowable Subject Matter

No claim is allowable.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

/Delia M. Ramirez/
Primary Examiner, Art Unit 1652